(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number
WO 2004/028479 A2

(51) International Patent Classification⁷: A61K

(21) International Application Number:
PCT/US2003/030907

(22) International Filing Date:
25 September 2003 (25.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/414,006   25 September 2002 (25.09.2002)   US

(71) Applicant *(for all designated States except US)*: GENEN-
TECH, INC. [US/US]; 1 DNA Way, South San Francisco,
CA 94080-4990 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BODARY, Sarah
[US/US]; 1520 Sand Hill Road, #205, Palo Alto, CA
94304 (US). CLARK, Hilary [US/US]; 495 Harkness
Avenue, San Francisco, CA 94134 (US). JACKMAN,
Janet [US/US]; 94 Patrick Way, Half Moon Bay, CA
94019 (US). SCHOENFELD, Jill [US/US]; 680 Spring
Creek Drive, Ashland, OR 97520 (US). WILLIAMS, P.,
Mickey [US/US]; 509 Alto Avenue, Half Moon Bay, CA
94019 (US). WOOD, William, I. [US/US]; 35 Southdown
Court, Hillsborough, CA 94010 (US). WU, Thomas, D.

[US/US]; 41 Nevada Street, San Francisco, CA 94110
(US).

(74) Agents: CARPENTER, David, A. et al.; Genentech, Inc.,
1 DNA Way, South San Francisco, CA 94080-4990 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
—   *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: NOUVELLES COMPOSITIONS ET METHODES DE TRAITEMENT DU PSORIASIS

(57) Abstract: La présente invention concerne des compositions contenant une nouvelle protéine ainsi que des méthodes d'utilisa-
tion desdites compositions pour le diagnostic et le traitement du psoriasis.

NOVEL COMPOSITIONS AND METHODS FOR THE TREATMENT OF PSORIASIS

5   Field of the Invention

The present invention relates to compositions and methods useful for the diagnosis and treatment of psoriasis.

Background of the Invention

10   Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation
15   or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

20   Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major
25   histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, *etc.* The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen -MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, *i.e.,* lymphokines, which
30   play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

Several diseases of the skin are correlated with an aberrant T cell response and to autoimmunity. Psoriasis is thought to be an autoimmune disease. Specifically, T-cells of the immune system recognize a protein in the skin and attack the area where that protein is found, causing the too-rapid growth of new skin
35   cells and painful, elevated, scaly lesions. These lesions are characterized by hyperproliferation of keratinocytes and the accumulation of activated T-cells in the epidermis of the psoriatic lesions. There are several forms of psoriasis; guttate is the one that most commonly occurs in children and teens. It is sometimes preceded by an upper respiratory infection. Guttate psoriasis is noncontagious and characterized by small drop-like lesions, usually scattered over the trunk, limbs and scalp. According to the National
40   Psoriasis Foundation, approximately seven million people in the United States have psoriasis. About 20,000

children are diagnosed with psoriasis annually, and many of the cases are attributed to upper respiratory infections. It is estimated that only about 1.5 million people with psoriasis actually seek treatment, primarily due to lack of or dissatisfaction with current treatments Although the initial molecular cause of disease is unknown, genetic linkages have been mapped to at least 7 psoriasis susceptibility loci (Psor1 on 6p21.3,

5   Psor2 on 17q, Psor3 on 4q, Psor4 on 1 cent-q21, Psor5 on 3q21, Psor6 on 19p13, and Psor7 on 1p). Some of these loci overlap with other autoimmune/inflammatory diseases including rheumatoid arthritis, atopic dermatitis, and irritable bowel disease. In this application, experiments determine that a gene is upregulated in psoriatic skin vs. normal skin.

Despite the above identified advances in psoriasis research, there is a great need for additional

10   diagnostic and therapeutic agents capable of detecting the presence of a psoriasis in a mammal and for effectively inhibiting this affliction. Accordingly, it is an objective of the present invention to identify polypeptides that are overexpressed in psoriasis as compared to normal skin, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of psoriasis in mammals.

15

Summary of the Invention

A.   Embodiments

The present invention concerns compositions and methods useful for the diagnosis and treatment of psoriasis in mammals, including humans. The present invention is based on the identification of proteins

20   (including agonist and antagonist antibodies) which are a result of psoriasis in mammals. Immune related diseases such as psoriasis may be treated by suppressing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Alternatively, molecules that suppress the immune response attenuate or reduce the immune

25   response to an antigen (e.g., neutralizing antibodies) can be used therapeutically where attenuation of the immune response would be beneficial (e.g., inflammation). Accordingly, the PRO polypeptides, agonists and antagonists thereof are also useful to prepare medicines and medicaments for the treatment of psoriasis. In a specific aspect, such medicines and medicaments comprise a therapeutically effective amount of a PRO polypeptide, agonist or antagonist thereof with a pharmaceutically acceptable carrier. Preferably, the

30   admixture is sterile.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprises contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native sequence PRO polypeptide. In a specific aspect, the PRO agonist or antagonist is an anti-PRO

35   antibody.

In another embodiment, the invention concerns a composition of matter comprising a PRO polypeptide or an agonist or antagonist antibody which binds the polypeptide in admixture with a carrier or excipient. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide or antibody. In a further aspect, when the composition comprises a psoriasis inhibiting molecule, the

40   composition is useful for: (a) reducing the amount of psoriasis tissue of a mammal in need thereof, (b)

2

inhibiting or reducing an auto-immune response in a mammal in need thereof, In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In another embodiment, the invention concerns a method of treating psoriasis in a mammal in need thereof, comprising administering to the mammal an effective amount of a PRO polypeptide, an agonist thereof, or an antagonist thereto.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody. In one aspect, the present invention concerns an isolated antibody which binds a PRO polypeptide. In another aspect, the antibody mimics the activity of a PRO polypeptide (an agonist antibody) or conversely the antibody inhibits or neutralizes the activity of a PRO polypeptide (an antagonist antibody). In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a monoclonal antibody, a single-chain antibody, or an anti-idiotypic antibody.

In yet another embodiment, the present invention provides a composition comprising an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. Preferably, the composition is sterile. The composition may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Alternatively, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the invention concerns an article of manufacture, comprising:

(a)   a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;

(b)   a container containing said composition; and

(c)   a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of an immune related disease. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

In yet another embodiment, the present invention concerns a method of diagnosing psoriasis in a mammal, comprising detecting the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample indicates the presence of psoriasis in the mammal from which the test tissue cells were obtained.

In another embodiment, the present invention concerns a method of diagnosing psoriasis in a mammal, comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and a PRO polypeptide, in the test sample; wherein the formation of said complex is indicative of the presence or absence of said psoriasis. The detection may be qualitative or quantitative, and may be performed in comparison with

monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence or absence of psoriasis in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected of having psoriasis.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a test sample of cells suspected of containing the PRO polypeptide to an anti-PRO antibody and determining the binding of said antibody to said cell sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

In another embodiment, the present invention concerns a psoriasis diagnostic kit, comprising an anti-PRO antibody and a carrier in suitable packaging. The kit preferably contains instructions for using the antibody to detect the presence of the PRO polypeptide. Preferably the carrier is pharmaceutically acceptable.

In another embodiment, the present invention concerns a diagnostic kit, containing an anti-PRO antibody in suitable packaging. The kit preferably contains instructions for using the antibody to detect the PRO polypeptide.

In another embodiment, the invention provides a method of diagnosing an psoriasis in a mammal which comprises detecting the presence or absence or a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of the PRO polypeptide in said test sample is indicative of the presence of psoriasis in said mammal.

In another embodiment, the present invention concerns a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the invention concerns a method for identifying a compound capable of inhibiting the activity of a PRO polypeptide comprising contacting a candidate compound with a PRO polypeptide under conditions and for a time sufficient to allow these two components to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits

4

2407/2777
FIGURE 2141

MRFMTLLFLTALAGALVCAYDPEAASAPGSGNPCHEASAAQKENAGEDPGLARQAPKPRKQRSSLLEKGLDGAKK
AVGGLGKLGKDAVEDLESVGKGAVHDVKDVLDSVL